REMARKS

Claims 1-9, 11, 12, 18, 20, 22, 24 and 28-47 are now in the case.

Consideration of this application and entry of the foregoing amendments are requested. The claims have been amended in view of the Office Action and to better define what the Applicants consider their invention as fully supported by an enabling disclosure.

Claims 10, 13, 14-17, 19, 21, 23, 25 and 26-27, cancelled in our previous response, remain cancelled without prejudice or disclaimer. Applicants reserve the rights to reintroduce the subject-matter thereof during the prosecution of further applications. Further support for the term "isolated" or "purified" in claims 1, 2, 8 and 31 can be found throughout the disclosure as originally filed. More specifically, further support for such amendments can be found, for example, in Example 1, termed "Procedure for isolation and purification of compound MV8612 (Figure 2)" at page 32, in Examples 2-4, in Example 5, at page 44, lines 8-18 and, in particular, between lines 13-15.

Further support for the amendments to claims 24, 35 and 39 can be found, for example, at page 19 in the figure legend of Figure 28; at page 6, between lines 26-27; at page 28, between lines 21 and 27, and in particular at line 25; and at page 52, lines 16-17.

Further support for claims 41, 42 and 43 relating to a prevention of a disease or condition associated with an overstimulation of R type calcium channels can be found throughout the disclosure. Exemplary support can be found at page 50, lines 25-29; at page 53, lines 2-5, 7-11 and lines 16-21; at page 57, between lines 14 and 17 and 21 to 23; at page 58, lines 23-25; at page 59, which relates to the *in vivo* prevention of inflammation at lines 3-6 and from line 28 to line 4 at page 60; as well as at page 61, lines 24-27. New claims 41, 42 and 43 are similar to claims 20, 22 and 40, respectively.

Further support for claims 44 and 45 which relate to cancer or tumor cells can also be found throughout the disclosure and in particular, at page 6, between lines 4 and 9, line 30, at page 7, line 2 and lines 18 to 20, at page 13, lines 3 to 20, in Figure 53, in which established T-lymphocyte cells were used; at page 20, lines 15 to 27, at page 29, lines 15 to 20, at page 51, lines 3 to 12 and at page 11, between lines 11 and 25.

Support for new claims 46 and 47 can be found for example in cancelled claims 13 and 15.

Finally, at page 52, it is stated at lines 12 to 17

> "Taken together, these results demonstrate that MV8608 blocked the R-type Ca^{2+} channel in all cell types used including the human osteoblast cancer cell lines (MG63 and FAOS-2), human VSM cells isolated from atherosclerotic patients, arterial and venous endothelial cells, endocardiac endothelial cells, T-lymphocytes and platelets (not shown) and spontaneously proliferative human aortic vascular smooth muscle cells, AOSMC-9 (Figure 28)."[emphasis added]

In view of the above and foregoing the Applicants respectfully submit, that the inhibition of cancer or tumor cells is clearly enabled, and therefore respectfully request that the Examiner withdraws his rejection of new claim 44 and 45, under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 10-40 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

More specifically, claims 11, 20, 22, 33, 34, 37, 38 and 40 have been rejected as being indefinite for using the term "prevention". The Examiner is of the opinion that "it is not clear whether prevention was achieved for a period of days, months, years or whether permanent prevention was achieved". Applicants respectfully traverse the rejection as follows:

Firstly, none of the rejected claims now contain the rejected terminology. Hence, the rejection of claims 11, 20, 22, 33, 34, 37, 38 and 40, for the use of the term "prevention" has been rendered moot. However, new claims 41, 42 and 43, which are based on claims 20, 22 and 40 but citing a method for "preventing" as opposed to "treating" are submitted herewith. The Examiner is respectfully referred to the overwhelming support for the term "preventing" found in the disclosure, as exemplified above at the beginning of the "Remarks" section. The Applicants respectfully submit that a person of ordinary skill in the art cognizant of the present specification and of the general state of the art at the time of filing the present application would consider the term "preventing" to be clear and definite. In view of the results presented in the instant invention, showing that (1) the compounds of the present invention can prevent for example inflammation, oedema, hypertension, or the like (e.g. Examples 11, 15 and 16; even in *in vivo* systems); and (2) through their action on the R-type Ca^{2+} channel, a person of ordinary skill in the art would not view the activity of the compounds as a permanent prevention, but rather as an activity which is dependent on the

time of action of the compound, its bio-availability when administered to a patient, its metabolic properties and the like. Such properties can be determined without undue experimentation and adapted by a person of ordinary skill wishing to prevent a disease or condition associated for example with an overstimulation of an R-type Ca^{2+} channel as recited in claims 41-43. The Applicants respectfully submit that a person of ordinary skill in the art would consider the term "prevention" as a clear, non-ambiguous" term. Applicants do not believe that the term "prevention" as used herein, could be understood as relating to "a vaccine".

Rejection of claims 11, 14 and 16 as being substantial duplicates, has been rendered moot by the cancellation of claims 14 and 16.

The Examiner objects to claims 10 and 14-27 as being improper "because a multiple dependent claim cannot depend from any other multiple dependent claims". Applicants believe that since the filing of the Preliminary Amendment, upon entry into the National Phase on March 28, 2000, no such improper dependencies are present. In any event, in view of the cancellation of claims 10, 14-17, 19, 21, 23 and 25-27, the Applicants respectfully submit that this objection has been rendered moot.

The Examiner's objection to the fact that "there is no antecedent basis in claim 1 for the compound in claim 28" has been rendered moot by the amendment of claim 28 so that it is now dependent on claim 2, instead of claim 1. Similarly, the lack of antecedent basis in claim 8 for the compound in claim 31 has been rendered moot by amending claim 31 so that it is now an independent claim.

The improper dependency of claim 29 because "it depends both from claim 2 and the figures" has been corrected by introducing the recitation of claim 2 into claim 29 which now only refers to the figures.

In view of the above and foregoing the Applicants respectfully request that the Examiner withdraws his rejection of claims 10-40, under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 102 (b) OR 35 U.S.C. § 103 (a)

Claims 1-40 have been rejected by the Examiner as being anticipated by or, in the alternative, as being obvious over Calixto *et al.*, or Neves et al.

The Applicants respectfully submit that in view of the amendments of claims 1, 2, 8, 29 and 31 so that they recite that the compounds are "isolated or purified" as suggested by the Examiner, that the anticipation or obviousness rejection has been rendered

moot. Applicants wish to point out, that prior to the present invention, the biological activity or structure of the compounds of the present invention were neither known nor suggested by the cited art. Prior to the present invention, the claimed compounds and their use as specific steady state R-type Ca^{2+} channel blockers were not known or suggested by the cited art.

In fact, prior to the present invention, the activity and structure of the isolated or purified compounds of the present invention could not be ascertained, since only crude fractions were used in the cited art.

In view of the above and foregoing, it is respectfully submitted that Calixto or Neves, together or separately, neither teach nor suggest the isolated and purified compounds of the present invention or their biological activity as R-type Ca^{2+} channel blockers.

The Examiner has also objected to the method claims, claiming that they "failed to specify a host to be treated and encompass prevention". The Applicants respectfully submit that in view of the amendments to the method claims, that this objection has been rendered moot.

CONCLUSIONS

The rejections of claims 1-40 are believed to have been overcome by the present remarks and by the amendments to the claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such an action is earnestly solicited.

In the event that there are any questions concerning the amendment or application in general, the Examiner is respectfully urged to telephone the undersigned so that the prosecution of the application may be expedited.

Authorization is hereby given to charge deposit account no. 13-2725 for any deficiencies or credit overpayments in connection with this response.

Respectfully submitted,

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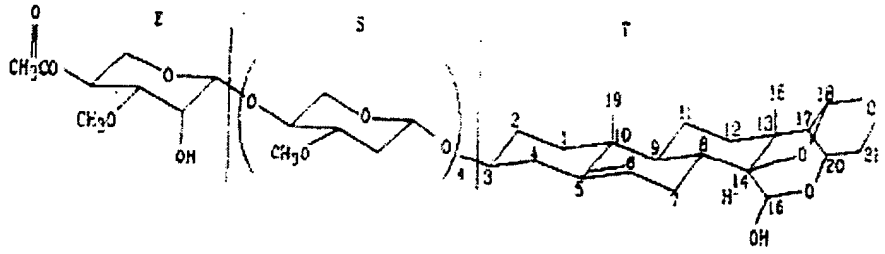
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 10, 13-17, 19, 21, 23 and 25-27 have been deleted.

Claims 1, 2, 8, 12, 18, 20, 22, 24, 28, 29, 31, 33-35 and 37-40 have been amended as follows: Underlines indicate insertions and brackets "[ ]" indicate deletions.

1. (Twice amended) [A] An isolated or purified compound having the formula:



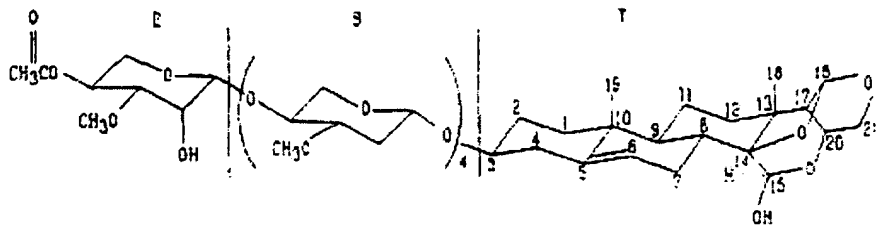
or a pharmaceutically acceptable salt thereof.

2. (Twice amended) [A] An isolated or purified compound having the formula EST, wherein:

a) E and S define a saponin oligosugar portion, with E defining the terminal sugar portion thereof; and

b) [and]T defines a steroid-like portion, wherein T is a pregnane-3β-ol derivative.

8. (Twice amended) [A] An isolated or purified R-type Ca2+ channel blocker having the formula:



or a pharmaceutically acceptable salt thereof.

10. (Delete) [The compound of claim 1, derivatized by one of alkylation, benzoylation, or glycosidation of the hydroxyl groups, chain of sugar extension or contraction.]

12. (Twice amended) The pharmaceutical composition of claim 11 for at least one of: (a) treating or blocking overstimulation of R-type Ca2+ channels associated with a disease or condition in a warm blooded animal[,or for]; (b) blocking or relieving side effects of a drug which overstimulate R-type CA2+ channels[, or for the prevention or treatment of]; and (c) treating a disease or condition in which a sustained elevation of [Ca]c, [Ca]n or R-type Ca2+ blocking is encountered.

13. (Delete) [The pharmaceutical composition of claim 11, wherein said compound is MV8612 and/or MV8608.]

14. (Delete) [A pharmaceutical composition for blocking or relieving side effects of a drug which overstimulate R-type Ca2+ channels comprising at least one compound of claim 1, together with a pharmaceutical carrier.]

15. (Delete) [The pharmaceutical composition of claim 14, wherein said compound is MV8608 and/or MV8612.]

16. (Delete) [A pharmaceutical composition for the prevention or treatment of a disease or condition in which a sustained elevation of [Ca]c, [Ca]n or R-type Ca2+ blocking is encountered, comprising at least one compound of claim 1, together with a pharmaceutical carrier.]

17. (Delete) [The pharmaceutical composition of claim 16, wherein said compound is MV8608 and/or MV8612.]

18. (Amended) A method for specifically inhibiting overstimulation of a R-type Ca^{2+} channel in a warm blooded animal in need of an inhibition of said overstimulation comprising an administration thereto of an effective amount of the compound of claim 1, together with a pharmaceutically acceptable carrier.

19. (Delete) [The method of claim 18, wherein said compound is MV8612 and/or MV8608.]

20. (Amended) A method of treating [or preventing] a disease or condition associated with an overstimulation of R-type Ca2+ channels without significantly affecting the basal activity thereof in a patient suffering from said disease or condition, comprising an administration thereto of an effective amount of the compound of claim 1, together with a pharmaceutically acceptable carrier.

21. (Delete) [The method of claim 20, wherein said compound is MV8612 and/or MV8608.]

22. (Amended) A method of treating [or preventing] a disease or condition associated with a sustained elevation of [Ca]c, [Ca]n, R-type Ca2+ blocking, and/or cytosolic and nuclear Ca2+ accumulation in a patient suffering from said disease or condition, comprising an administration thereto of a therapeutically effective amount of a R-type Ca2+ channel blocker compound according to claim 1, together with a pharmaceutically acceptable carrier.

23. (Delete) [The method of claim 22, wherein said compound is MV8612 and/or MV8608.]

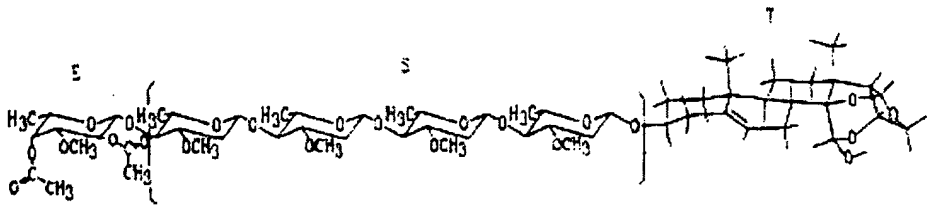
24. (Amended) A method for decreasing spontaneous cell proliferation [of cancer and tumor cells] comprising [an incubation thereof with] administering to said cell an effective amount of a [R-type Ca2+ channel blocker] compound according to claim 1, together with a pharmaceutically acceptable carrier.

25. (Delete) [The method of claim 24, wherein said compound is MV8612 and/or MV8608.]

26. (Delete) [The compound of claim 1, wherein said compound is capable of blocking cytosolic and nuclear Ca2+ overload.]

27. (Delete) [The compound of claim 26, wherein said compound is MV8612 and/or MV8608.]

28. (Amended) The compound of [Claim1] claim 2, having the formula:



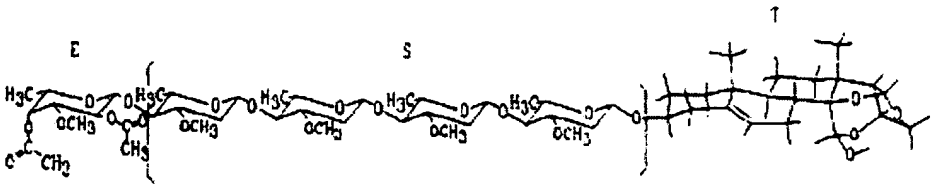
or a pharmaceutically acceptable salt thereof.

29. (Amended) [The] An isolated or purified compound [of claim 2] having the formula EST, wherein: [T has]

a) E and S define a saponin oligosugar portion, with E defining the terminal sugar portion thereof; and

b) T defines a steroid-like portion, wherein T is a pregnane-3β-ol derivative having the structure shown in Figure 1A, 1B, 1C, 1D, 1E, 1F, 1G or 1H.

31. (Amended) An isolated or purified R-type Ca2+ channel blocker, [of Claim 8,] having the formula:



or a pharmaceutically acceptable salt thereof.

33. (Amended) A method of treating [or preventing] a disease or condition associated with an overstimulation of R-type Ca2+ channels without significantly affecting the basal activity thereof in a patient suffering from said disease or condition, comprising an administration thereto of an effective amount of the compound of claim 2, together with a pharmaceutically acceptable carrier.

34. (Amended) A method of treating [or preventing] a disease or condition associated with a sustained elevation of [Ca]c, [Ca]n,] R-type Ca2+ blocking, and/or cytosolic and nuclear Ca2+ accumulation in a patient suffering from said disease or condition, comprising an administration thereto of a therapeutically effective amount of a R-type Ca2+ channel blocker compound according to claim 2, together with a pharmaceutically acceptable carrier.

35. (Amended) A method for decreasing spontaneous cell proliferation [of cancer and tumor cells] comprising [an incubation thereof with] administering to said cell an effective amount of a [R-type Ca2+ channel blocker] compound according to claim 2, together with a pharmaceutically acceptable carrier.

37. (Amended) A method of treating [or preventing] a disease or condition associated with an overstimulation of R-type Ca2+ channels without significantly affecting the basal activity thereof in a patient suffering from said disease or condition, comprising an administration thereto of an effective amount of the compound of claim [1]28, together with a pharmaceutically acceptable carrier.

38. (Amended) A method of treating [or preventing] a disease or condition associated with a sustained elevation of [Ca]c, [Ca]n, R-type Ca2+ blocking, and/or cytosolic and nuclear Ca2+ accumulation in a patient suffering from said disease or condition, comprising an administration thereto of a therapeutically effective amount of a R-type Ca2+ channel blocker compound according to claim [1] 28, together with a pharmaceutically acceptable carrier.

39. (Amended) A method for decreasing the spontaneous cell proliferation [of cancer and tumor cells] comprising, administering to said cell [an incubation thereof with] an effective amount of a [R-type Ca2+ channel blocker] compound according to claim [1] 28, together with a pharmaceutically acceptable carrier.

40. (Amended) A method of treating [or preventing] a disease or condition associated with an overstimulation of R-type Ca2+ channels without significantly affecting the basal activity thereof in a patient suffering from said disease or condition, comprising an administration thereto of an effective amount of a compound having the structure shown in Figure 1A, 1B, 1C, 1D, 1E, 1F, 1G or 1H, together with a pharmaceutically acceptable carrier.

Claims 41-47 are new.